· 临床研究 ·

常染色体隐性遗传增强蓝视锥细胞综合征中国汉族一家系临床和遗传学特征分析

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【摘要】 目的　分析增强蓝视锥细胞综合征（ESCS）一家系的临床表型及致病基因。 **方法**　采用家系调查研究方法，收集 2021 年 6—9 月于河南省立眼科医院就诊的中国汉族疑似 ESCS 一家系，该家系共 3 代 8 人，其中患者 1 例。对先证者进行全面的眼科检查，包括视力、斜视程度、眼前节和眼底情况、视网膜自发荧光、荧光素眼底血管造影、全视野视网膜电图（ERG）、多焦 ERG、光相干断层扫描，以评估表型。收集该家系成员外周血样本，提取 DNA，采用全外显子组测序（WES）技术进行测序，筛查致病基因及变异位点。采用 Sanger 测序验证变异位点是否与临床表型共分离。采用 SIFT、Polyphen2、MutationTaster 在线工具分析变异位点有害性；采用美国医学遗传学及基因组学会（ACMG）遗传变异分类标准与指南分析变异位点致病性；采用 SIFT 分析变异位点对应氨基酸序列保守性。 **结果**　该家系符合常染色体隐性遗传方式。先证者自幼夜盲、远视、调节性内斜视、周边视网膜色素样沉积、视网膜劈裂、ERG 明视反应以大振幅波为主。WES 检测发现 1 个复合杂合变异 *NR2E3* 5 号外显子 c.671C>T：p.S224L 和 6 号外显子 c.955G>A：p.E319K，Sanger 测序验证结果显示变异位点与临床表型共分离。2 个变异位点均为错义变异，在 gnomAD 数据库东亚人群中变异频率为 0；SIFT、Polyphen2、MutationTaster 预测基因产物有害；其中 c.671C>T 变异在疾病数据库 ClinVar 中有意义不明记录，c.955G>A 变异为未报道新位点。ACMG 遗传变异分类标准与指南显示 2 个变异均为临床意义未明变异。2 个变异位点对应的氨基酸序列在不同物种中均具有高度保守性。 **结论**　该家系符合 ESCS 的临床特征和遗传学诊断。本研究发现了 *NR2E3* 基因 2 个未报道的变异位点 c.671C>T：p.S224L 和 c.955G>A：p.E319K。

【关键词】 增强蓝视锥细胞综合征；家系；基因检测；全外显子组测序；基因型；表现型；*NR2E3* 基因
基金项目： 河南省医学科技攻关计划项目（LHGJ20200069）
DOI：10.3760/cma.j.cn115989-20210902-00490

Clinical and genetic characteristics of a Han Chinese family with autosomal recessive enhanced S-cone syndrome

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[**Abstract**] **Objective**　To analyze the clinical phenotypes and pathogenic gene of a Han Chinese family with enhanced S-cone syndrome (ESCS). **Methods**　The method of pedigree investigation was adopted. A suspected ESCS Han Chinese family including 8 members of 3 generations was recruited in Henan Eye Hospital from June to September 2021. There was one patient in the family. A thorough ophthalmic examination of the proband was carried out to evaluate the phenotypes, including visual acuity, degree of strabismus, anterior segment and fundus, autofluorescence imaging, fluorescein fundus angiography, full-field electroretinogram (ERG), multifocal ERG, optical coherence tomography. DNA was extracted from peripheral blood samples from the proband and family members. The pathogenic gene and variation were screened by whole exome sequencing (WES). The variation and co-segregation were verified by Sanger sequencing. The deleteriousness of the variation was analyzed by SIFT, Polyphen2 and MutationTaster. The pathogenicity of the variation was evaluated in accordance with the American College of Medical Genetics and Genomics (ACMG) Standards and Guidelines. The analysis of amino acid sequence conservation was performed by SIFT. This study adhered to the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Henan Eye Hospital (No. HNEECKY-2017[6]). Written informed consent was obtained from each

subject. **Results** This pedigree was consistent with autosomal recessive inheritance. The proband had clinical features such as night blindness, hyperopia, accommodative esotropia, peripheral retinal pigmentation, retinoschisis, and photopic ERG responses dominated by large-amplitude waves. Variations including a compound heterozygous variation, c. 671C>T: p. S224L on exon 5 and c. 955G>A: p. E319K on exon 6 of *NR2E3* were identified by WES. The variations were confirmed to be consistent with co-segregation. The both loci were missense variations, the variation frequency of which was 0 in the East Asian population via the gnomAD database. The variations were predicted to be deleterious by SIFT, Polyphen2 and MutationTaster. The c. 671C>T variation was recorded with unknown significance in ClinVar database, and the c. 955G>A variation was an unreported new locus. According to the ACMG Standards and Guidelines, the both variations were labeled as with uncertain clinical significance, and the corresponding amino acid sequences were highly conservative across multiple species. **Conclusions** This family has the clinical characteristics of ESCS and meets the genetic diagnosis criteria. Two novel variations in *NR2E3* gene, c. 671C>T: p. S224L and 955G>A: p. E319K, are found.

[**Key words**] Enhanced S-cone syndrome; Pedigree; Genetic testing; Whole exome sequencing; Genotype; Phenotype; *NR2E3* gene

Fund program: Henan Medical Science and Technology Project (LHGJ20200069)

DOI: 10. 3760/cma. j. cn115989-20210902-00490

增强蓝视锥细胞综合征(enhanced S-cone syndrome, ESCS)又称蓝锥细胞增强症,是一种少见的常染色体隐性遗传性视网膜疾病,通常由感光细胞特异表达的核受体转录因子(nuclear receptor subfamily 2, group E, member 3, *NR2E3*)基因突变造成[1]。ESCS 患者临床表现为夜盲、高度远视、调节性内斜视、黄斑区视网膜劈裂、视网膜电图(eletroretinogram, ERG)明视反应以 S 视锥细胞介导的大振幅波为主等。Marmor 等[2]于 1990 年首次报道 8 例 ESCS 患者,目前国内未见相关病例报道。本研究采用全外显子组测序(whole exome sequencing, WES)对中国汉族可疑 ESCS 一家系进行基因检测,确定该家系的致病突变位点并分析患者临床表型,为 ESCS 的临床诊断提供参考。

1　资料与方法

1.1　一般资料

采用家系调查研究方法,纳入 2021 年 6—9 月在河南省立眼科医院就诊的中国汉族 ESCS 一家系,收集该家系成员 3 代 6 人的临床资料,包括 5 位表型正常成员和 1 例患者。同期纳入 60 名在河南省立眼科医院体检的健康受试者作为正常对照,正常对照均排除眼部及全身疾病。本研究遵循《赫尔辛基宣言》,研究方案经河南省立眼科医院伦理委员会审核批准[批文号:HNEECKY-2017(6)],所有受检者均了解本研究目的并自愿签署知情同意书。

1.2　方法

1.2.1　家系成员临床检查　详细询问并记录家族史、婚育史及全身其他疾病史。对家系中患者及表型正常成员进行眼部检查。采用对数视力表测定受检者裸眼视力和最佳矫正视力;采用角膜映光法检查双眼斜视度;采用同视机检查双眼斜视度和眼外肌功能;采用裂隙灯显微镜检查眼前节;采用双目间接检眼镜检查眼底;采用全景眼底照相仪(英国欧堡公司)检查受检者视网膜自发荧光;采用 Octopus 视野计(瑞士 Haag-Streit 集团)检查视野;采用光相干断层扫描仪 v1. 33. 1[中国视微影像(河南)科技有限公司]检查受检眼黄斑部结构;采用眼科激光眼底血管造影机(德国海德堡公司)进行受检眼荧光素眼底血管造影(fluorescein fundus angiography, FFA)检查;采用 RETIport 视觉电生理系统(德国 Roland 公司)记录全视野 ERG。按照国际临床视觉电生理协会 2015 年公布的记录标准化方案,依次进行暗适应的 4 项检查:(1)暗适应 0. 01 ERG,光刺激强度为 0. 01 (cd·s)/m^2;(2)暗适应 3. 0 ERG,光刺激强度为 3. 0 (cd·s)/m^2;(3)暗适应 3. 0 振荡电位,光刺激强度为 3. 0 (cd·s)/m^2;(4)暗适应 10. 0 ERG,光刺激强度为 10. 0 (cd·s)/m^2。明适应 10 min 后,行明适应的 2 项检查:(1)明适应 3. 0 ERG,光刺激强度为 3. 0 (cd·s)/m^2;(2)明适应 3. 0 闪烁 ERG,光刺激强度为 3. 0 (cd·s)/m^2;全部测试由同一医生进行。对混合光反应的 a、b 波,明视 ERG a、b 波和 30 Hz 闪烁光 ERG 反应波形进行分析;采用 RETIport 视觉电生理系统记录受检眼多焦视网膜电图(multifocal eletroretinogram, mfERG),使用 61 个六边形刺激,每个循环 47 s,分析各环对应视网膜区域的 N1 和 P1 波平均振幅密度。

1.2.2　家系致病基因的 WES 检测　对先证者及其胞兄、父亲、外公、舅舅进行 WES 检测,重点分析与视网膜疾病及眼球发育相关基因。

1.2.2.1 基因组 DNA 提取　采集受检者外周静脉血各 5 ml，采用磁珠法血液基因组 DNA 提取试剂盒（北京 Tiangen Biotech 公司）提取基因组 DNA，采用 Qubit 3.0 荧光计（Qubit 双链 DNA 检测试剂盒，美国 Invitrogen 公司）定量基因组 DNA 的质量浓度及总量（质量浓度≥50 ng/μl，$A_{260}/_{280}$ 为 1.8～2.0，DNA 总量≥6 g）。采用琼脂糖凝胶电泳检测提取基因组 DNA 的纯度及完整性。

1.2.2.2 基因组文库构建　采用 Covaris M220 Focused-ultrasonicator 对质检合格的基因组 DNA 样本进行片段化回收处理，采用 Integrated DNA Technologies（美国 IDT 公司）的 xGen® Exome Research Panel v2.0 试剂盒对人类全基因外显子组区域进行液相捕获建库。

1.2.2.3 WES 及 Sanger 测序验证　将捕获的 DNA 文库通过 Illumina HiseqX 测序平台（美国 Illumina 公司）对人类全基因外显子组序列进行 2×150 bp 的双末端测序，获得原始测序数据。质控原始数据，合格后将结果通过 Burrows Wheeler Aligner（BWA version 0.7.16a，http://bio-bwa.sourceforge.net/）软件与 UCSC 人类基因组参考序列 GRCh38 进行比对，生成的 bam 文件采用 Genome Analysis Tool Kit（GATK，version 4.0.8.1）软件进行变异检测分析，主要包括单核苷酸多态性、插入和缺失等，根据测序深度和变异质量进行变异过滤（变异 Quality 除以 Depth 的比值，即 QD 值需大于 2，变异位点深度至少达到 20X），最后利用 ANNOVAR（http://annovar.openbioinformatics.org/）软件进行变异位点注释，获得候选致病突变位点，筛选出的所有候选致病突变位点经 Sanger 验证以排除假阳性，并在家系成员中验证是否与临床表型共分离，最终确定致病基因突变位点。

1.2.3 变异位点致病性及保守性分析　采用 SIFT、Polyphen2、MutationTaster 在线工具分析变异位点有害性；采用美国医学遗传学及基因组学会（American College of Medical Genetics and Genomics，ACMG）遗传变异分类标准与指南分析变异位点致病性；采用 SIFT 分析变异位点对应氨基酸序列保守性。

2　结果

2.1　该 ESCS 家系临床特点分析

该家系符合常染色体隐性遗传方式（图 1）。先证者Ⅲ-1，21 岁，以自幼夜盲、视近时眼球内斜、视疲劳为主诉就诊；验光结果示右眼 +4.50 DS－0.75 DC×5°＝0.7，左眼 +5.00 DS－1.25DC×175°＝0.3；双眼斜视度为 0～+10°；交替遮盖内－正（图 2）。

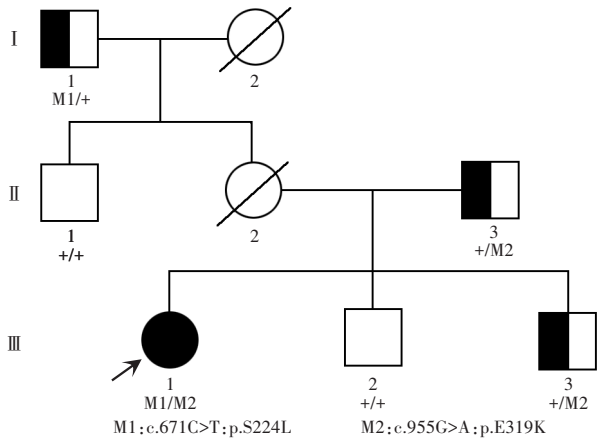

图 1　ESCS 家系图　□：正常男性；○：正常女性；◧：男性携带者；●：女性患者；/：已故；↗：先证者

Figure 1　Pedigree of the ESCS family　□：normal male；○：normal female；◧：male carrier；●：female patient；/：deceased；↗：proband

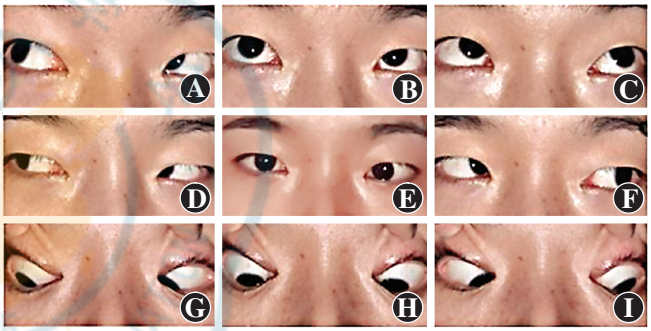

图 2　先证者双眼眼位图　调节性内斜视 9 个方位眼位图，正前方眼位图可见左眼角膜映光点位于瞳孔颞侧，其他诊断眼位未见肌肉麻痹征象落后　A：右上方眼位　B：正上方眼位　C：左上方眼位　D：右侧眼位　E：正前方眼位（第一眼位）　F：左侧眼位　G：右下方眼位　H：下方眼位　I：左下方眼位

Figure 2　Cardinal gaze positions of the proband　In the 9 cardinal positions to diagnose accommodative esotropia, the corneal refractive spot on the temporal side of left pupil in primary position was observed, and no signs of muscle paralysis was seen in other positions　A: right and up gaze　B: up gaze　C: left and up gaze　D: right gaze　E: primary position　F: left gaze　G: right and down gaze　H: down gaze　I: left and down gaze

双眼球运动检查示右眼下斜肌轻度亢进，上斜肌功能轻度减弱；双眼隐性水平性眼球震颤；双眼前节检查未见明显异常，双眼视盘边界清，色泽正常，周边视网膜可见色素样沉积，黄斑区上方血管弓处出现淡黄色病灶，视网膜色素上皮缺损（图 3）；双眼血管弓内黄斑区自发荧光增强（图 4）；OCT 检查可见黄斑区外丛状层视网膜层间出现低反光小腔，呈虫噬样（图 5）；FFA 检查显示视网膜血管及视盘形态正常，黄斑区未见荧光素渗漏（图 6）；双眼视野检查显示环形暗点和旁中心暗点（图 7）；ERG 表现为暗适应下低强度光（0.01）刺激记录不到波形，高强度光（3.0）刺激记录到大而慢的反应波，随背景光强度增加（明适应），该波形无变化，暗适应曲线的视锥

细胞反应曲线之后不出现视杆细胞反应曲线，30 Hz 条件下呈非常小且延迟的波形（图 8）；mfERG 显示 1 环 N1 和 P1 波振幅密度轻度下降、波形相对正常，随离心度增加潜伏期延迟；mfERG 二维图显示左眼中心峰向颞侧偏移，呈旁中心注视（图 9）。先证者母亲Ⅱ-2 因脑出血于 2018 年去世，去世前眼部情况正常；先证者胞兄Ⅲ-2 和Ⅲ-3（25 岁、28 岁）、父亲Ⅱ-3（52 岁）、外祖父Ⅰ-1（78 岁）及舅舅Ⅱ-1（56 岁）双眼眼位正常，眼底检查和全视野 ERG 均未发现明显异常。该家系符合家系共分离。

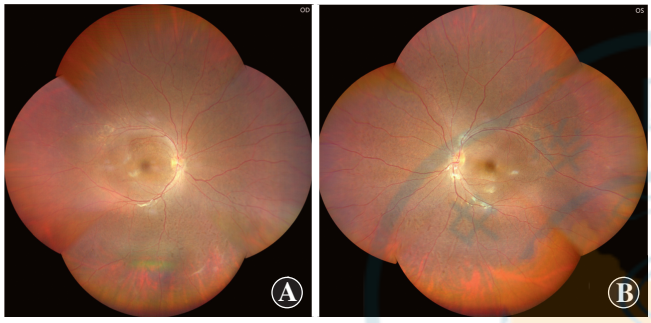

图 3　先证者双眼广角眼底照相拼图　视盘色正界清，周边视网膜色素沉积，黄斑上方血管弓处可见淡黄色病灶　A：右眼　B：左眼

Figure 3　Wide-angle fundus images of the proband　Clear optic disc, peripheral retinal pigmentation, yellowish lesions around vessel arches above the macula were seen　A: right eye　B: left eye

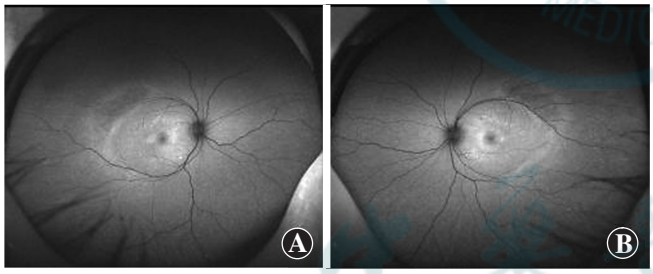

图 4　先证者双眼眼底自发荧光图像　双眼血管弓内黄斑区可见强荧光　A：右眼　B：左眼

Figure 4　Fundus autofluorescence images of the proband　Strong fluorescence was seen in the macular area within the vascular arch in both eyes　A: right eye　B: left eye

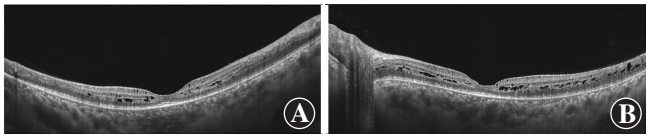

图 5　先证者双眼黄斑 OCT 图像　黄斑区近外丛状层视网膜层间出现密集的不规整低反射小腔　A：右眼　B：左眼

Figure 5　OCT images of the proband　Dense irregular hyporeflective cavities were seen between retinal layers near the macular outer plexiform layer　A: right eye　B: left eye

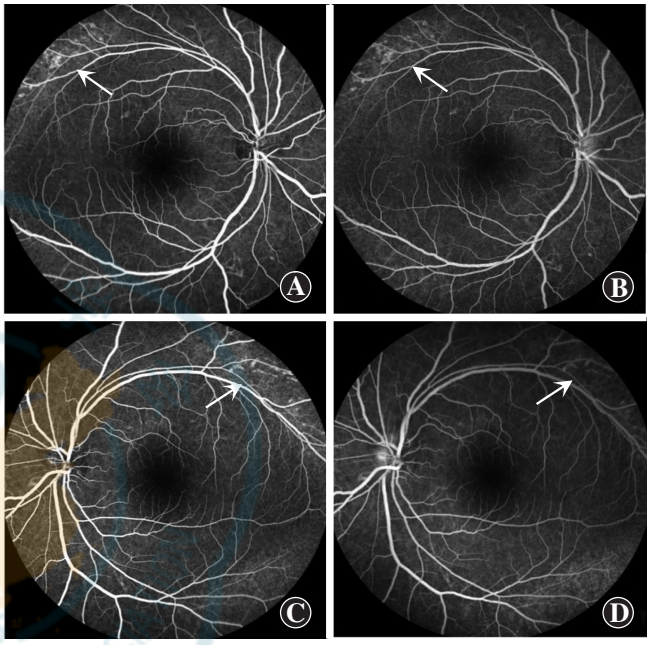

图 6　先证者双眼 FFA 图像　双眼颞上方血管弓可见斑片状弱荧光（箭头），后期无明显增强，黄斑区未见荧光素渗漏　A、B：右眼　C、D：左眼

Figure 6　FFA images of the proband　Patchy weak fluorescence (arrow) was seen in the superior temporal beyond the vascular arch in both eyes, not significantly enhanced in the late stage, and no fluorescein leakage was found in the macula　A, B: right eye　C, D: left eye

2.2　该 ESCS 家系基因检测结果分析

先证者 *NR2E3* 基因存在 1 个复合杂合变异，为 5 号外显子 c.671C>T：p.S224L 和 6 号外显子 c.955G>A：p.E319k，2 个变异位点均为错义变异，其中 c.671C>T 变异导致 NR2E3 蛋白第 224 位的丝氨酸改变为亮氨酸，c.955G>A 变异导致第319位的谷氨酸改变为赖

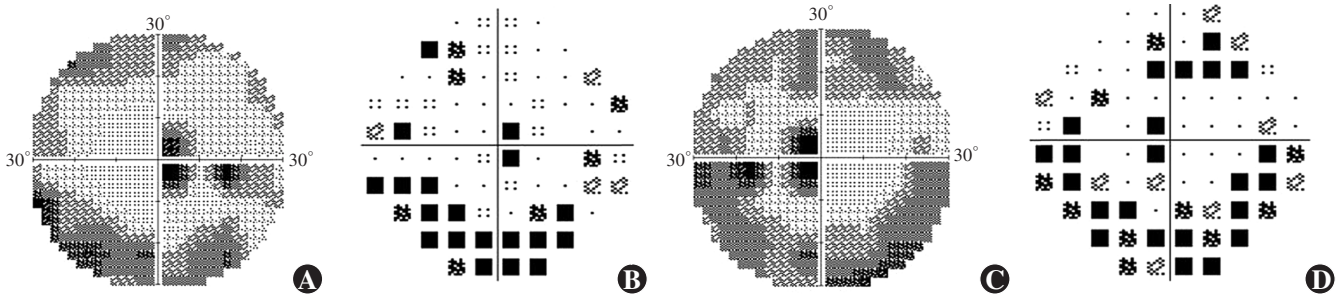

图 7　先证者双眼视野图像　可见双眼环形暗点和旁中心暗点　A：右眼灰度图　B：右眼模式偏差图　C：左眼灰度图　D：左眼模式偏差图

Figure 7　Visual test results of the proband　Ring scotomas and paracentral scotomas were seen in both eyes　A: Gray map of right eye　B: Pattern deviation map of right eye　C: Gray map of left eye　D: Pattern deviation map of left eye

氨酸(图 10)。c. 671C>T 变异在 gnomAD 数据库东亚人群中的频率为 0,在 ClinVar 数据库中有意义未明的记录,未见文献报道。c. 955G>A 变异在 gnomAD 数据库东亚人群及 ClinVar 中均无收录,未见文献报道。SIFT、Polyphen2、MutationTaster 预测 2 个变异产物均有害。ACMG 遗传变异分类标准与指南显示 2 个变异均为临床意义未明变异。家系分析发现 c. 955G>A 变异遗传自先证者父亲,由于其母亲去世,不能确定 c. 671C>T 变异的来源。对人(*Homo sapiens*)、牛(*Bos taurus*)、黑猩猩(*Pan troglodytes*)、小鼠(*Mus musculus*)、斑马鱼(*Danio rerio*)、鸡(*Gallus gallus*)的该变异位点对应的氨基酸序列进行比对,显示第 224 个和第 319 个位点在不同物种中均具有高度保守性(图 11),发生变异后致病可能性较高,结合临床表型,确诊为由 *NR2E3* 基因变异引起的 ESCS。

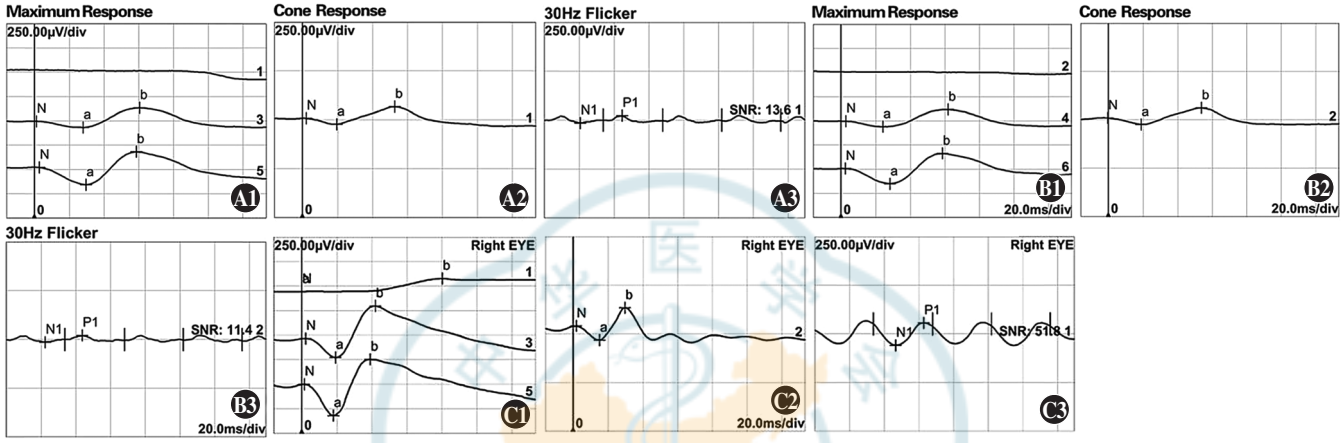

图 8　先证者双眼全视野 ERG 与正常人 ERG 对照表现　A1、B1:先证者右眼、左眼杆锥混合反应　暗适应 0. 01 ERG 无波形,暗适应 3. 0 ERG a 波振幅中-重度降低,b 波振幅中度降低且潜伏期延长,暗适应 10. 0 ERG a、b 波振幅中度降低且潜伏期延长　A2、B2:先证者右眼、左眼杆锥反应明适应 3. 0 ERG　a、b 波振幅轻度降低且潜伏期延长　A3、B3:先证者右眼、左眼 30 Hz 闪光刺激反应明适应 3. 0 ERG　N1-P1 波振幅中度降低　C1、C2、C3:正常对照杆锥混合反应、杆锥反应明适应 3. 0 ERG 和闪光刺激反应明适应 3. 0 ERG

Figure 8　Comparison of ERG between proband and normal control　A1, B1: Mixed rod-cone response of right and left eye of proband　It showed mixed rod-cone response without waveform in scotopic 0. 01 ERG, moderate to severe reduction of a-wave, moderate decrease of b-wave and increased b-wave latency in scotopic 3. 0 ERG, moderate reduction of a- and b-wave as well as increased a- and b-wave latency in scotopic 10. 0 ERG　A2, B2: Photopic 3. 0 ERG of right (A2) and left eye (B2) of proband　Mixed rod-cone response with mild reduction of a- and b-wave as well as increased a- and b-wave latency　A3, B3: Moderately reduced N1-P1 amplitude in the right eye (A3) and left eye (B3) in photopic 3. 0 flicker ERG (30 Hz)　C1, C2, C3: Mixed rod-cone response, scotopic 3. 0 ERG, and photopic 3. 0 flicker ERG in normal control

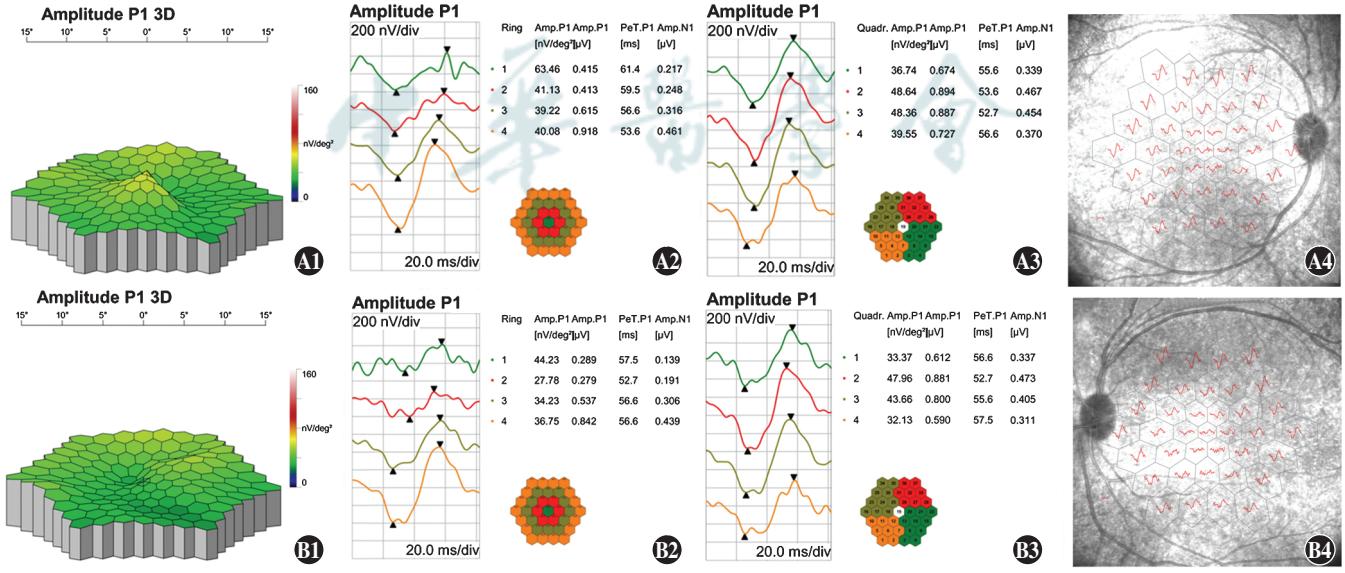

图 9　先证者双眼 mfERG 检查图　A1:右眼 P1 波 3D 显示中心注视　B1:左眼 P1 波 3D 显示旁中心注视,偏颞侧　A2、A3、A4、B2、B3、B4:可见 1 环 N1 和 P1 波振幅密度轻度下降、波形相对正常,而随离心度的增加,潜伏期延迟　A:右眼　B:左眼

Figure 9　mfERG results of the proband　A1: A 3D display of P1 wave showed central fixation in the right eye　B1: A 3D display of P1 wave showed paracentral fixation with temporal deviation in the left eye　A2, A3, A4, B2, B3, B4: In ring 1, amplitude density of N1 and P1 waves decreased with relatively normal waveform, and latency delayed as centrifugation increased　A: right eye　B: left eye

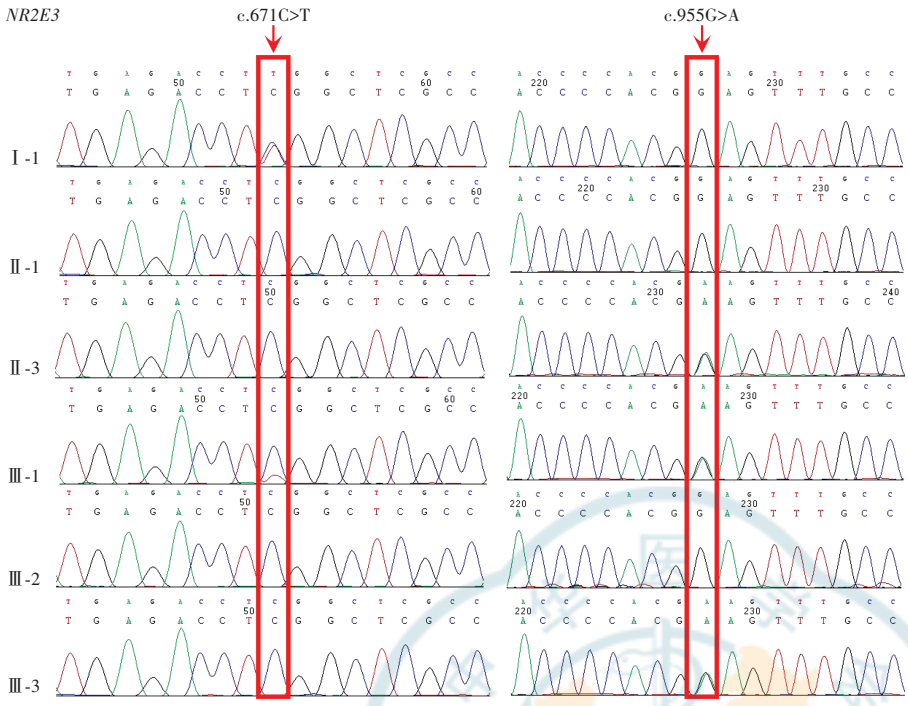

图 10　该 ESCS 家系 Sanger 测序图　先证者 *NR2E3* 基因存在复合杂合变异，即 c. 671C>T/c. 955G>A

Figure 10　Sanger sequencing map of the ESCS family　A compound heterozygous variation c. 671C>T/c. 955G>A was detected in *NR2E3* gene in the proband

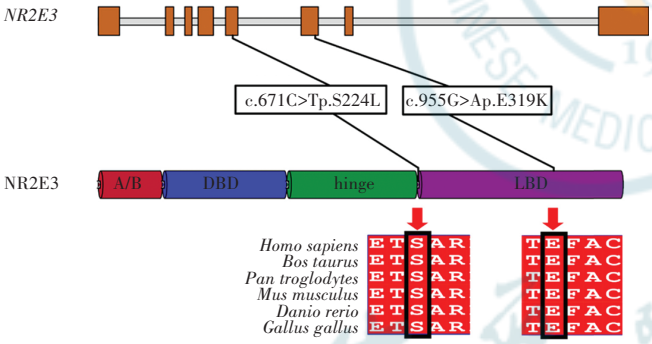

图 11　*NR2E3* 基因结构及变异位点保守性分析　NR2E3 第 224 个和第 319 个氨基酸位点在人（*Homo sapiens*）、牛（*Bos taurus*）、黑猩猩（*Pan troglodytes*）、小鼠（*mus musculus*）、斑马鱼（*Danio rerio*）、鸡（*Gallus gallus*）的氨基酸序列中均高度保守

Figure 11　*NR2E3* structure and conservation analysis of variation　Loci 224 and 319 of NR2E3 were highly conserved in amino acid sequences across *Homo sapiens*, *Bos taurus*, *Pan troglodytes*, *mus musculus*, *Danio rerio* and *Gallus gallus*

3　讨论

本研究先证者 2 岁发现夜盲，诊断为夜盲症。入院后经 ERG 及 OCT 检查显示患者视杆、视锥细胞功能受损，黄斑区视网膜层间多个小劈裂腔，双眼为调节性内斜视，暗适应功能障碍，临床表型与 ESCS 症状相符。基因测序发现，先证者 *NR2E3* 基因存在 2 个未报道的 c. 671C>T：p. S224L、c. 955G>A：p. E319K 变异位点，该复合杂合变异导致了患者 ESCS 的发生。

PubMed 数据库中共检索到 78 篇与 ESCS 相关的文献。既往报道的 *NR2E3* 基因变异导致的 ESCS 文献中有 84 个突变位点，包括 58 个错义突变、15 个剪切突变、6 个移码突变、4 个缺失突变、1 个无义突变，其中 3 个位于 N 端的 A/B 结构域，24 个位于 DNA 结合域，5 个位于铰链区，37 个位于配体结合域，c. 119－2A>C 和 c. 932G>A（p. R311Q）是其中常见的 2 个突变位点[3-29]。

ESCS 是一种由染色体 15q23 核受体基因 *NR2E3* 变异导致的常染色体隐性遗传视网膜营养不良，患者在儿童时期眼底正常或在视网膜色素上皮有少量白点，视网膜团块状色素沉着多发生于 9～11 岁，黄斑囊样改变不伴有 FFA 荧光素渗漏或劈裂[30-31]。人类视网膜有短波敏感型（S，蓝）、中波敏感型（M，绿）和长波敏感型（L，红）视锥光感受器。大多数遗传性视网膜营养不良视杆细胞和视锥细胞呈进展性退行性改变。然而，ESCS 呈现短波视锥细胞功能增强，中波及长波视锥细胞功能受损、视杆细胞功能记录不到。因此该患者暗适应下低强度光（0. 01）刺激 ERG 各波记录不到，高强度光（3. 0）刺激记录到大而慢的反应波，随背景光强度增加（明适应）该波形无变化。人 *NR2E3* 基因变异导致常染色体显性和常染色体隐性视网膜色素变性、Goldmann-Favre 综合征、色素集群视网膜变性以及 ESCS 等多种视网膜疾病[16,32-37]。ESCS 与 Goldmann-Favre 综合征临床表型有相似之处，后者被认为是前者的严重类型[37]。*NR2E3* 基因编码 1 条包含 410 个氨基酸、相对分子质量为 45 000 的多肽。NR2E3 蛋白包含氨基端的 A/B 结构域、DNA 结合结构域、铰链区以及羧基端的配体结合结构域，其中 DNA 结合结构域负责结合靶基因的启动子，配体结合结构域负责与配体结合，但 NR2E3 的配体还未明确；铰链区为 NR2E3 的核定位信号[8,38-39]。NR2E3 缺失的 rd7 小鼠视杆细胞能够正常发育、分化和成熟[1,40-43]，*NR2E3* 基因在人和斑马鱼中是保守的，*NR2E3* 基因变异的斑马鱼视杆前体细胞不能分化为成熟的视杆细胞，ESCS 患者视杆细胞功能在早期即严重损伤[44]，出现夜盲症状。

ESCS、先天性静止性夜盲、无色素性视网膜色素变性早期均表现为夜视力差，轻中度视力下降，视野正常，仅依靠主诉和眼底表型难以鉴别，但各自具有不同的 ERG 特征，当不能明确鉴别时应行 ERG 检查，同时结合基因检测进一步明确诊断。ESCS 表型有很高的异质性，许多视网膜细胞退化和 *NR2E3* 基因变异的因果关系尚不清楚，不同物种中 *NR2E3* 基因变异后表型也有一定差异，导致 NR2E3 的功能研究具有一定困难。本家系先证者 21 岁，眼底病情发展变化有赖于长期的随访观察和更深入的遗传学研究。

本研究发现了 *NR2E3* 基因中 2 个未报道的突变位点 c. 671C>T：p. S224L 和 c. 955G>A：p. E319K，丰富了常染色体隐性遗传 ESCS 的基因变异谱，为研究其致病机制提供了有用信息，同时可以为临床开展遗传咨询和生育指导提供参考依据。

利益冲突　所有作者均声明不存在任何利益冲突

作者贡献声明　蒋永强：直接参与选题、设计试验、实施研究、采集数据、起草文章；郭浩轶：酝酿和设计试验，对文章知识性内容进行审阅和修改；李杰、陈慷：分析/解释数据

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（收稿日期：2022-03-20　修回日期：2022-08-29）

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论著或综述文稿正文请撰写中英文摘要。原创性论著文稿要求为结构式摘要，包括目的（Objective）、方法（Methods）、结果（Results）和结论（Conclusions）4 个要素，摘要应能够回答以下问题：（1）为什么进行这项研究。（2）主要用什么方法进行研究。（3）获得什么主要结果。（4）通过研究得出什么结论等。其中目的部分为本课题对所涉及的研究内容及亟待解决的问题设立的目标。方法部分应提供研究对象、样本量、分组情况、各组的干预情况、与研究相适应的观察或检测指标，获得结局指标的手段和设备等。临床研究请说明是前瞻性研究、回顾性研究还是观察性研究。结果部分请客观描述研究的主要发现，包括主要的形态学检查表现、相关的关键性或主要的量化资料以及相应的统计学比较结果，须写明统计学量值及其概率值。结论部分请提出与本研究论据直接相关的、必然的推论，避免得出过度推测性、评价性和扩大化的结论。摘要请用第三人称客观表述，不列图表，不引用文献，不加评论和解释。英文摘要应与中文摘要内容相对应，但为了对外交流的需要，可以略详细。英文摘要应包括论文文题（正体）及全部作者姓名（汉语拼音，姓在前，首字母大写，名在后，首字母大写，双字连写。如：Yin Xiaohui）、标准化的单位名称、城市名称（汉语拼音）、邮政编码及国家名称（全部为斜体）。并请在另起一行处提供通信作者姓名的汉语拼音和 Email 地址，如 *Corresponding author: Yin Xiaohui, Email: xiaohuih@126.com*。专家述评或综述类文稿请撰写指示性中英文摘要，摘要内容应包含研究涉及的概念、研究的目的、综述资料的来源、复习的文献量、研究的新发现或应用领域、综合的结果和结论及其意义等必要的信息。

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